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Smoking, Clopidogrel, and Mortality in Patients with Established Cardiovascular Disease

Jeffrey S. Berger, MD, MS[1], **Deepak L. Bhatt, MD, MPH**[2], **Steven R. Steinhubl, MD**[3], **Mingyuan Shao, MS**[4], **P. Gabriel Steg, MD**[5], **Gilles Montalescot, MD**[6], **Werner Hacke, MD**[7], **Keith A. Fox, MBChB**[8], **A. Michael Lincoff, MD**[4], **Eric J. Topol, MD**[9], and **Peter B. Berger, MD**[10] **for the CHARISMA Investigators**

[1] New York University School of Medicine, New York, NY; 1 University of Pennsylvania, Philadelphia, PA [2] VA Boston Healthcare System and Brigham and Women's Hospital, Boston, MA [3] The Geisinger Clinic, Danville, PA and The Medicines Company, Zurich Switzerland [4] Cleveland Clinic, Cleveland, OH [5] INSERM U-698, Université Paris 7 and AP-HP, Paris, France [6] Institut de

Corresponding Author: Deepak L. Bhatt, MD, MPH, VA Boston Healthcare System and Brigham and Women's Hospital, Boston, MA, Phone: 1-857-203-6840, Fax: 1-857-203-5550, DLBHATTMD@alum.mit.edu.

Clinical Perspective

Clopidogrel is metabolized in the Cytochrome P450 (CYP) pathway to its active metabolite and smoking is an inducer of CYP1A2. Recent *in vitro* data suggest that smoking influences the platelet inhibitory effect of clopidogrel, yet the relationship between clopidogrel, smoking and clinical outcomes is incompletely understood. The objectives of this study were two-fold: first, to evaluate the relationship between smoking status (current, former and never) on all-cause, cardiovascular, and cancer mortality in patients with established cardiovascular disease, and second, to investigate the safety and efficacy of clopidogrel versus placebo stratified by smoking status. Among patients with established cardiovascular disease, smoking status is a strong independent risk factor for all cause mortality, cardiovascular mortality, cancer mortality, cardiovascular events, and bleeding risk. A significant interaction existed between current smokers and clopidogrel use for the outcomes of all-cause and cardiovascular mortality. Clopidogrel was most effective in reducing all-cause and cardiovascular mortality, while simultaneously increasing the risk of bleeding in current smokers, a finding not observed in former or never smokers. The current analysis extends and reinforces the increase in total and cause-specific mortality caused by smoking, as well as the increase in bleeding in a population with established cardiovascular disease. The data suggest an important relationship between smoking status and the safety and efficacy of clopidogrel therapy. Further studies are needed to investigate this possibility.

Disclosures

Dr Jeffrey Berger reports receiving research support from Astra Zaneca (modest) and has received honoraria for advisory board participation from The Medicines Company (modest).

Dr. Bhatt has received research grants (to the institution, significant) from: Bristol-MyersSquibb, Eisai, Ethicon, Heartscape, sanofi aventis, The Medicines Company. Dr. Bhatt has served as a consultant (honoraria waived or donated for > past two years, modest) for: Arena, Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, Cardax, Centocor, Cogentus, Daiichi-Sankyo, Eisai, Eli Lilly, Glaxo Smith Kline, Johnson & Johnson, McNeil, Medtronic, Millennium, Molecular Insights, Otsuka, Paringenix, PDL, Philips, Portola, Sanofi Aventis, Schering Plough, Takeda, The Medicines Company, Vertex.

Dr. Steinhubl is currently a full-time employee of The Medicines (>$10,000) and as such have stock options (<$10,000)

Dr Topol has served as a consultant to Daiichi-Sankyo, Portola Pharmaceuticals and Sanofi-Aventis (each for more than $10,000).

Dr Steg reports receiving research support from sanofi aventis (significant), and honoraria as consultant or speaker from AstraZeneca (significant), Astellas (modest), Bayer (modest), Boehringer-Ingelheim (modest), BMS (modest), Endotis (modest), GSK (modest), MSD (modest), Medtronic (modest), Nycomed (modest), sanofi-aventis (significant), Servier (significant), Takeda (modest), The Medicines Company (modest).

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Dr Lincoff reports receiving research funding (to the institution) from Sanofi-Aventis, Astra Zeneca, BMS, The Medicines Company, Eli Lilly, Johnson and Johnson, Schering-Plough, Scios, Takeda, Daiichi-Sankyo (each for more than $10,000).

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Dr Peter Berger served as a consultant to PlaCor, Accumetrics, and Lilly/Daiichi Sankyo, (each for less than $10,000)

Cardiologie–CHU Pitié-Salpêtrière, Paris, France [7] University of Heidelberg, Heidelberg, Germany [8] University and Royal Infirmary of Edinburgh, Edinburgh [9] Scripps Clinic, La Jolla, CA [10] Geisinger Medical Center, Danville, PA

Abstract

Background—Smoking increases platelet aggregability, and the degree of platelet inhibition by clopidogrel on ex vivo platelet function tests. Whether smoking status affects the relationship between clopidogrel and clinical outcomes is unknown.

Methods and Results—We evaluated the relationship between smoking status (current smoker (CS), former smoker (FS), and never smoker (NS)) and treatment with clopidogrel on the risk of all-cause, cardiovascular, and cancer mortality among the 12,152 participants from the CHARISMA trial with established cardiovascular disease. Current smoking was associated with an increase in all-cause (adjusted hazard ratio [HR] 2.58, [1.85–3.60]), cardiovascular (HR 2.26, [1.48–3.45]), and cancer mortality (HR 4.16, [2.46–7.03]) compared to NS. The impact of clopidogrel and mortality differed by smoking status (P for interaction = 0.018 for current smokers). Among CS, clopidogrel was associated with a reduction in all-cause mortality (HR 0.68, [0.49–0.94]); clopidogrel did not reduce all cause mortality among FS (HR 0.95, [0.75–1.19]) or NS (HR 1.14, [0.83–1.58]). A similar pattern was noted for cardiovascular mortality. As expected, no relationship was observed between clopidogrel and cancer mortality by smoking status. The risk of bleeding seemed to differ according to smoking status; randomized clopidogrel was associated with a significantly increased hazard of severe or moderate bleeding (HR 1.62, P=0.04) among CS, but a smaller and nonsignificant increase among NS (HR 1.31, P=0.15).

Conclusion—Clopidogrel therapy may be more effective, but with a greater bleeding risk in CS than in patients who are not smokers. Further studies are needed to investigate this possibility.

Keywords

Smoking; Clopidogrel; Mortality; Cardiovascular disease

More than 80 million people have cardiovascular disease in the United States[1]. Although recent data suggest improving outcomes in this high-risk population[2], the overall mortality rate remains quite high and cardiovascular disease is the number one killer in the United States[1]. Considerable research has been directed at improving outcomes in this population[3]. Because of its high associated morbidity and mortality, the influence of smoking in this population remains a major topic of interest and concern[4–6]. Cigarette smoking has a number of adverse effects which influence the cardiovascular system and overall health[5]. Smoking causes endothelial dysfunction, dyslipidemia, and increased platelet activation leading to a prothrombotic state[7–9]. Smoking increases insulin resistance and diabetes[10, 11], and is associated with increases in emerging biomarkers, including fibrinogen, factor VII, homocysteine, and C-reactive protein[12, 13]. Thus, a number of mechanisms may help explain the heightened risk of cardiovascular disease in smokers.

Many reports have consistently demonstrated a significant adverse relationship between smoking and mortality[14]. Risk induced by smoking increases dramatically with the number of cigarettes smoked daily[15]. Data from several reports noted a significant relationship between total and cause specific mortality in male and female smokers[16–18]. A recent report from the Nurses Health Study demonstrated that excess vascular mortality may rapidly decrease upon cessation, but lung disease mortality may take up to 20 years[19]. The relationship between smoking status, total mortality, and cause-specific mortality in patients with established cardiovascular disease in the current era is less well established.

Recent laboratory data suggest that smoking influences the antiplatelet effect of clopidogrel[20]. Cigarette smoking is an inducer of CYP1A2[21], a hepatic enzyme involved in the metabolism of clopidogrel[22]. Clopidogrel has been reported to result in greater inhibition of platelet aggregation in smokers than non-smokers[20], suggesting that the pharmacodynamic response to clopidogrel may be modified by smoking. In studies that assessed the variability of platelet response to clopidogrel, smokers were less likely to be hyporesponders than non-smokers[23]. Whether smoking affects clinical outcomes in patients receiving clopidogrel remains uncertain.

The objectives of this study were two-fold: first, to evaluate the relationship between smoking status (current, former and never) on all-cause, cardiovascular, and cancer mortality in patients with established cardiovascular disease, and second, to investigate the safety and efficacy of clopidogrel versus placebo according to smoking status. We hypothesized that, in patients with established cardiovascular disease, current smokers would be at greatest risk for all-cause mortality, cardiovascular mortality and cancer mortality. Since smoking appears to augment the antiplatelet effects of clopidogrel, we postulated that clopidogrel would have a greater benefit and higher bleeding risk than placebo in current smokers than in former smokers or those who had never smoked.

Methods

The design, methods, and primary results of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial have been described in detail previously[24]. To briefly summarize, CHARISMA was a prospective, multicenter, double-blind, randomized, placebo-controlled trial comparing clopidogrel 75 mg/day versus placebo long-term in patients at high risk for cardiovascular events. All patients also received aspirin (75 to 162 mg/day). After a median follow-up of 28 months, clopidogrel was no more effective than placebo at reducing the rate of myocardial infarction, stroke or cardiovascular death25.

For this study, we analyzed the impact of smoking status on mortality, cardiovascular events, and severe or moderate bleeding in subjects with established cardiovascular disease. Additionally, we evaluated the differential treatment effect (interaction) of clopidogrel versus placebo according to smoking status. Since smoking status was also used as an entry criterion for inclusion into the study for patients without established cardiovascular disease, patients without established cardiovascular disease were excluded from this analysis. We divided the remaining 12,152 patients with established cardiovascular disease into 3 groups, according to smoking status: current smokers, former smokers, and patients who never smoked. Current smokers were defined by a person smoking at least 1 cigarette per day during the month before enrollment. Former smokers were defined by a person smoking at least 1 cigarette per day at any time prior to the month before enrollment. Rates of permanently discontinuing clopidogrel did not differ by smoking status (current smoker – 19.4%, former smoker – 18.9%, never smoker – 18.2%, Chi-Square p-value = 0.51). The median follow-up time was the same as in the main study (28 months).

We compared the relationship between current smokers versus never smokers, former smokers versus never smokers, and current smokers versus former smokers on all-cause mortality, mortality sub-type, cardiovascular events, and risk of severe or moderate bleeding. In addition, we compared the relative efficacy of clopidogrel versus placebo on all-cause, cardiovascular, and cancer mortality according to smoking status. Additionally, we compared the relative safety of clopidogrel versus placebo on severe or moderate bleeding (determined by the GUSTO criteria26) according to smoking status. These events were adjudicated by the Cleveland Clinic Clinical Events Adjudication Committee.

Statistical Analysis

All data analyses were performed on the intention-to-treat population. Hypothesis tests were done using 2-sided tests at the 5% significance level. Baseline characteristics were compared with chi-square tests for discrete and analysis of variance for continuous variables. The adverse outcomes were compared using a two-sided log-rank test and were plotted using cumulative Kaplan-Meier estimates of the event rates. Hazard ratios and their 95% confidence intervals was estimated using Cox proportional hazards model.

Multivariable Cox proportional hazards models were created to assess the relationship of the smoking status and the adverse outcomes after adjusting for baseline demographic and clinical history variables. Indicator variables of current smoker, former smoker versus never smoker were created to represent the smoking data. An indicator variable of Europe versus all others was created for geographic region. Demographic data and baseline characteristics were entered into a multivariable Cox model for variable selection using bootstrap resampling (500 iterations and a p-value criterion of 0.1 for retention). Those having a 50% or more probability of retention were considered reliable and were entered into a second Cox model with the model selection procedure of stepwise selection or backward elimination. The significance level to enter and keep a variable was set at 0.05. These risk factors as well as the smoking indicator variables met the proportional hazards assumption by plotting the log of the negative log of their estimated survival distribution, $\log(-\log(S(t)))$, versus time. The linearity assumption was assessed and satisfied for all the continuous variables by plotting the logit of the events against the continuous variable. The selected covariates from the two model selection methods were compared to choose an optimal multivariable Cox model for each individual clinical endpoint.

Univariable interactions were tested in a Cox proportional hazards model, incorporating terms for randomized treatment, smoking status, and the treatment-by-smoking status interaction, to assess if treatment effect differed for current smokers versus never smokers and formers smokers versus never smokers. Multivariable interactions were further analyzed by adding covariates of baseline characteristics into the model.

Since this analysis is exploratory and meant to primarily be hypothesis generating, no adjustments for multiple comparisons were made. All statistical analyses were performed with SAS software (version 9.1.3; SAS Institute, Cary, North Carolina).

Results

Of the 12,152 patients included in this analysis, 2419 (19.9%) were current smokers, 6260 (51.5%) were former smokers, and 3473 (28.6%) never smoked. The median time of quitting smoking for former smokers was 11 years (range, 0 to 69 years; mean 14.3 ±13.4 years). Table 1 shows the baseline characteristics of the study participants by smoking status. Compared with never smokers, current smokers were younger, less frequently female and more likely to be Caucasian. Current smokers were less likely to have a history of hypertension, diabetes, heart failure, or prior revascularization, but were more likely to have peripheral arterial disease.

Mortality

All-cause mortality significantly differed according to smoking status: current smoker – 6.1%, former smoker – 4.6%, never smoker – 4.3%, P=0.001 (Figure 1). After multivariable adjustment, current smokers had an increased hazard of all-cause mortality (hazard ratio (HR) 2.58, 95% confidence interval (CI) 1.85 – 3.60, P<0.01) compared with never smokers; whereas the hazard associated with former smokers compared with those who never smoked did not reach statistical significance (HR 1.25, 95% CI 0.93 – 1.68, P=0.14) (Table 2). In multivariable adjusted modeling, cardiovascular mortality (HR 2.26, 95% CI 1.48 – 3.45, P<0.01) and cancer

mortality (HR 3.56, 95% CI 1.96 – 6.46, P<0.001) were elevated in current smokers compared with never smokers. Former smokers compared with never smokers were at increased hazard for cardiovascular mortality (HR 1.29, 95% CI 0.90 – 1.84, P=0.17) and cancer mortality (HR 2.08, 95% CI 1.24 – 3.49, P<0.01), although the former was not statistically significant.

Cardiovascular disease

The incidence of cardiovascular events (MI/stroke/cardiovascular death) was 8.4% in current smokers, 7.1% in former smokers and 7.3% in never smokers (P=0.05). Compared with those who never smoked, current smokers had an increased adjusted hazard of cardiovascular events (HR 1.49, 95% CI 1.21 – 1.82, P<0.01). No excess hazard was seen for former smokers (HR 1.00, 95% CI 0.84 – 1.17, P=0.95). Current smokers had a greater hazard of stroke (HR 1.56, 95% CI 1.16 – 2.10, P<0.01); for MI, the excess risk did not reach statistical significance (HR 1.37, 95% CI 0.96 – 1.95, P=0.08). No significant difference was observed between former smokers and never smokers for MI or stroke (Table 2).

Bleeding

Severe or moderate bleeding occurred in 3.1% of current smokers, 3.0% of former smokers and 3.3% of never smokers (P=0.64). After multivariable adjustment, current smokers had a higher hazard of severe or moderate bleeding (adjusted HR 1.48, 95% CI 1.09 – 2.00, P=0.01) compared with never smokers. No statistically significant increased hazard for severe or moderate bleeding was observed for former smokers (HR 1.06, 95% CI 0.83 – 1.34, P=0.64).

Current versus former smokers

After removing all patients who never smoked from the analysis, we performed multivariable adjustments to compare current versus former smokers. Current smokers were at increased risk for all-cause mortality (HR 1.72, 95% CI 1.39 – 2.12, P<0.01), cardiovascular mortality (HR 1.62, 95% CI 1.23 – 2.13, P<0.01), cancer mortality (HR 1.69, 95% CI 1.21 – 1.82, P<0.01), cardiovascular events (HR 1.56, 95% CI 1.31 – 1.86, P<0.01), MI (HR 1.39, 95% CI 1.03 – 1.882, P=0.03), stroke (HR 1.56, 95% CI 1.18 – 2.05, P<0.01), and severe or moderate bleeding (HR 1.38, 95% CI 1.05 – 1.83, P=0.02) compared with former smokers (Figure 2).

Clopidogrel

Finally, we assessed whether smoking status had any influence on the effect of clopidogrel. In the overall cohort, all-cause mortality was 4.6% with clopidogrel and 5.0% with placebo (HR 0.91, 95% CI 0.78 – 1.07, P=0.27). A significant interaction existed between current smokers and clopidogrel use for the outcome of all-cause mortality (P=0.018). Among current smokers, clopidogrel was associated with a reduction in all-cause mortality (HR 0.68, 95% CI 0.49 – 0.94). No reduction in all-cause mortality was noted for either former smokers (HR 0.95, 95% CI 0.75 – 1.19) or patients who never smoked (HR 1.14, 95% CI 0.83 – 1.58). Similarly, a significant interaction existed between current smokers and clopidogrel for the outcome of cardiovascular mortality (P for interaction =0.037) (Figure 3). As would be expected, no significant interaction was noted for cancer mortality (P=NS).

The effect of clopidogrel on reducing cardiovascular events (MI/stroke/cardiovascular death) did not differ according to smoking status (P for interaction=NS). Clopidogrel was associated with a non-significant reduction in cardiovascular events in current smokers (HR 0.93, 95% CI 0.71 – 1.22), former smokers (HR 0.83, 95% CI 0.69 – 1.00), and never smokers (HR 0.92, 95% CI 0.72 – 1.17). Although no significant interaction was noted, the benefit of clopidogrel versus placebo on the risk of cardiovascular death or MI was greater in current smokers (HR 0.82, 95% CI 0.58 – 1.15) than in former smokers (HR 0.92, 95% CI 0.74 – 1.15) or those who never smoked (HR 1.01, 95% CI 0.74 – 1.37).

The relationship between clopidogrel versus placebo on severe or moderate bleeding is illustrated in Figure 4. The risk of severe or moderate bleeding was increased in all smoking categories. However, despite the lack of a significant interaction between smoking and bleeding (P for interaction = NS), the magnitude of the risk of severe or moderate bleeding with clopidogrel seemed to be related to smoking status. Specifically, clopidogrel was associated with a statistically significant increase in the risk of bleeding in current smokers (HR 1.62, 95% CI 1.02 – 2.58, P=0.04). Among those who never smoked, however, the increase in risk associated with clopidogrel was not statistically significant (hazard ratio, 1.31, 95% CI 0.90 – 1.90, P=0.15).

Discussion

Among patients with established cardiovascular disease, smoking status is a strong independent risk factor for all cause mortality, cardiovascular mortality, cancer mortality, cardiovascular events, and bleeding risk. Current smokers were at higher risk for each endpoint analyzed than former smokers and those who never smoked. Interestingly, former smokers had similar outcomes as those who had never smoked, except for higher cancer mortality. These data also indicate that the benefit and risk of clopidogrel may be related to smoking status. Clopidogrel was most effective in reducing all-cause and cardiovascular mortality, while simultaneously causing an increase in the risk of bleeding in current smokers, a finding not observed in former or never smokers.

We believe our data have clinical relevance for several reasons. Although smoking is known to influence total and cause specific mortality in the general population[16–18], data in patients with cardiovascular disease is inconsistent[27–31]. In fact, several reports of patients following a myocardial infarction or percutaneous revascularization described a lower adverse event rate among smokers, described as the “smoker’s paradox”[27–29]. Nevertheless, despite the younger age and considerably lower risk of current smokers at the time of enrollment in this study, smoking has a widespread negative effect on health. The current analysis extends and reinforces the increase in total and cause-specific mortality caused by smoking, as well as the increase in bleeding in a population with established cardiovascular disease.

In our analysis, former smokers had a risk of all-cause mortality, cardiovascular mortality and bleeding risk similar to those who never smoked. In contrast, the risk of cancer mortality remained elevated in former smokers compared with those who never smoked. These data suggest that the high risk of all-cause and cardiovascular mortality and severe or moderate bleeding subsides after smoking cessation, while the risk of cancer mortality persists for a longer period of time. Recent data from the Nurses Health Study is consistent, finding that cardiovascular mortality decreases rapidly upon smoking cessation, whereas cancer related mortality may take up to 20 years[19].

The data suggest an important relationship between smoking status and the safety and efficacy of clopidogrel therapy. A formal test of heterogeneity of the treatment effect of clopidogrel on all-cause mortality and cardiovascular mortality was statistically significant, suggesting that the benefit of clopidogrel may not be identical across smoking categories. The present finding indicates that the effect of clopidogrel in reducing all-cause and cardiovascular mortality was greatest among current smokers and that the benefit diminished significantly in former smokers and never smokers. As expected, the effect of clopidogrel on cancer mortality was neutral and was not modified by clopidogrel use. Surprisingly, the relationship between clopidogrel and cardiovascular events was not significantly modified by smoking. Nevertheless, the apparent benefit of clopidogrel in reducing fatal cardiovascular events in current smokers suggests a real and plausible association. Overall, this data in accordance with others[32], supporting recent ex vivo data which showed greater platelet inhibition by clopidogrel in current smokers

compared with never smokers[20]. These data, combined with this clinical analysis, suggests that factors such as smoking modify the benefit of clopidogrel. Cigarette smoking induces CYP1A2 activity[21], a hepatic enzyme involved in the metabolism of clopidogrel. Thus, the greater platelet inhibition demonstrated by Bliden and colleagues[20] and the clinical differences observed in the current study may be explained via the induction of CYP1A2. An alternative explanation for the association between smoking and clopidogrel may be partly explained by the lower release of tissue plasminogen activator in current smokers[8]. Current smokers with impaired endogenous fibrinolysis may benefit most from antiplatelet therapy, an observation noted in thrombolytic therapy and coined the "smoker's paradox"[33]. Since clopidogrel is known to increase bleeding, we evaluated whether smoking would modulate the excess bleeding risk with clopidogrel. Although no significant interaction was detected for bleeding risk and smoking, current smokers had the greatest risk of bleeding from clopidogrel. This excess risk was attenuated in a stepwise fashion in former and current smokers.

Limitations

There are several important limitations of this analysis. First, it should be reemphasized that this post hoc subgroup analysis ought to be considered hypothesis-generating. Our analyses of smoking status are based on a single base-line determination that may have changed over the study period; we do not have data on smoking following enrollment. However, misclassifications of smoking status would probably have attenuated the true association between current smokers and adverse events; thus, these results may represent an underestimate of the risk associated with current smoking.

Conclusions

Among patients with established cardiovascular disease, current smokers are at increased hazard for all-cause, cardiovascular and cancer specific mortality, cardiovascular events, and severe or moderate bleeding. These data also suggest that the benefit and risk of clopidogrel may be modified by smoking status, thus providing additional evidence to support the hypothesis that the antiplatelet effect of clopidogrel may be enhanced in current smokers.

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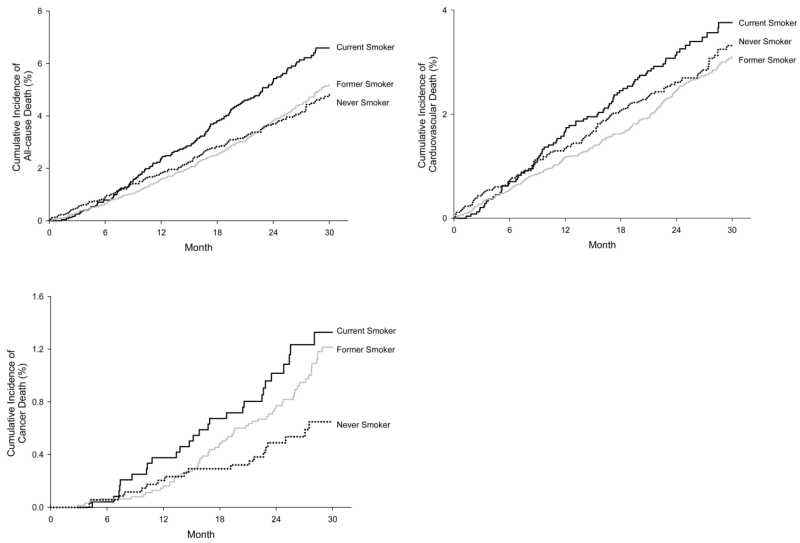

Figure 1. Kaplan-Meier curves of cardiovascular events stratified by smoking status

Cumulative incidence of all-cause mortality, cardiovascular mortality, and cancer mortality stratified by smoking status.

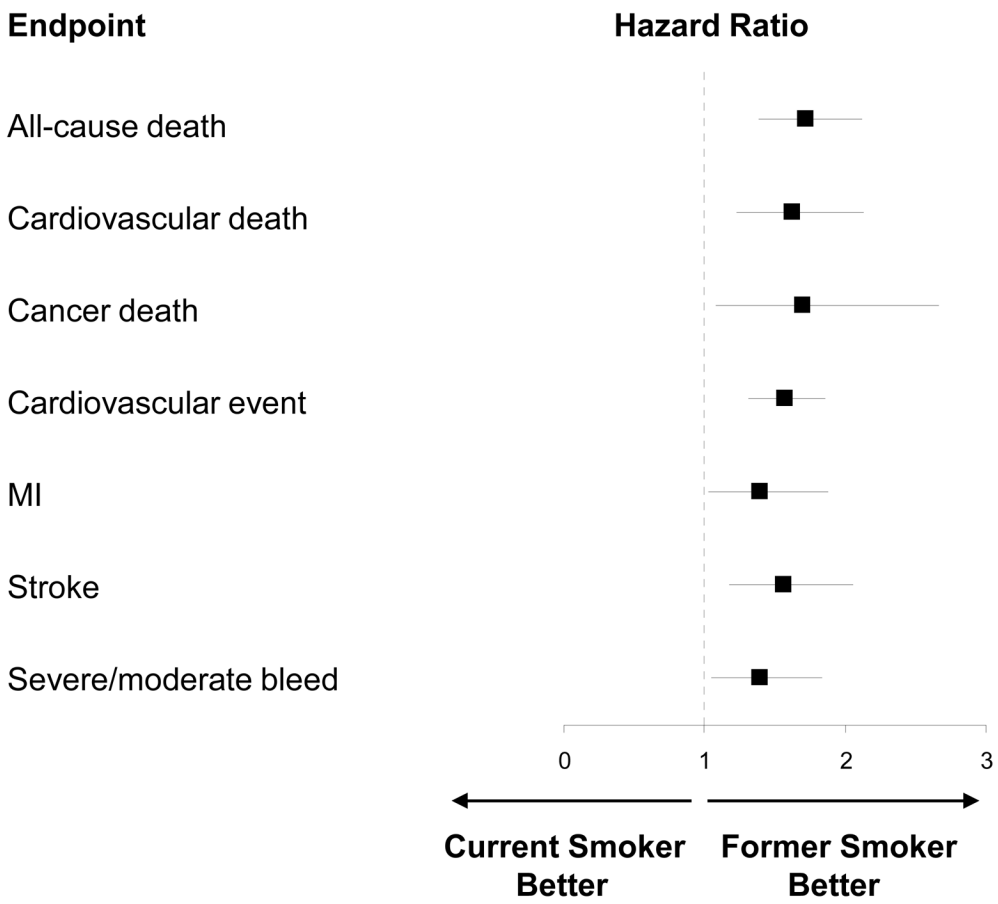

Figure 2. Adjusted hazard ratio for the cardiovascular endpoints in current smokers versus former smokers

Hazard ratio and 95% confidence interval adjusting for the cardiovascular risk factors for the efficacy and safety endpoints for current smokers versus former smokers in the ever smoking patients (n=8,679) with established cardiovascular disease.

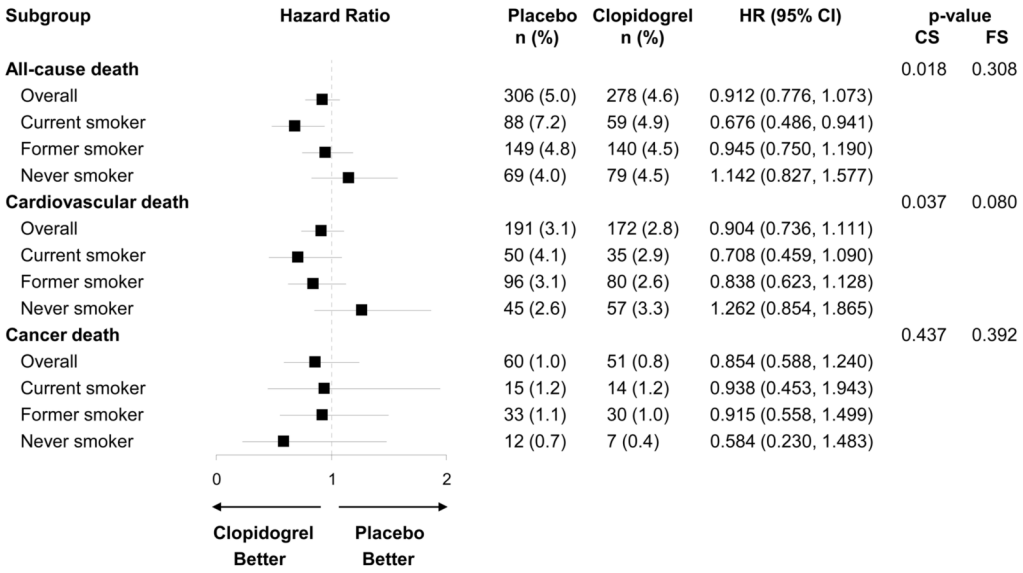

Figure 3. Subgroup analysis of clopidogrel versus placebo on a) all-cause mortality, b) cardiovascular mortality, and c) cancer mortality by smoking status

Frequencies, cumulative event rates, hazard ratios, 95% confidence intervals, and p-values for the multivariable interaction between the treatment effect and the smoking subgroup variables (presented as indicator variables for current smoking and former smoking, respectively) are shown for the risk of adverse events associated with clopidogrel by smoking status among the 12,152 patients with established cardiovascular disease enrolled in CHARISMA. CS, current smoking. FS, former smoking.

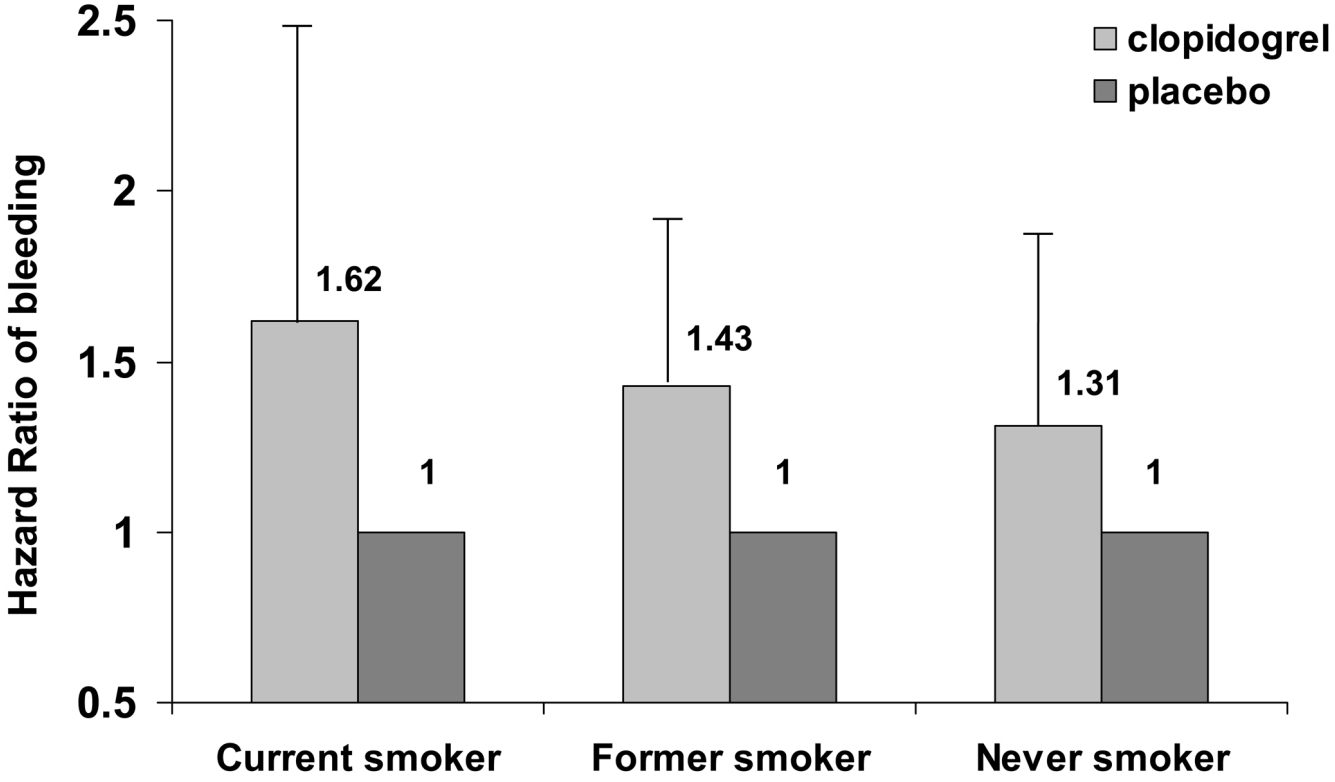

Figure 4. Hazard ratio of severe or moderate bleeding in randomized assignment to clopidogrel versus placebo therapy according to smoking status

The increase in the risk of severe or moderate bleeding associated with the use of clopidogrel was 62 percent in current smokers (3.9% vs 2.4%, P=0.04), 43 percent in former smokers (3.5% vs 2.5%, P=0.02), and 31 percent in never smokers (3.7% vs 2.8%, P=0.15) (P for interaction >0.05).

Table 1

Baseline demographics by smoking status

	Current Smokers (n=2419)	Former Smokers (n=6260)	Non- Smokers (n=3473)	P- value
Demographics				
Age (yr, mean ± SD)	60.4 ± 8.5	64.3 ± 9.4	66.1 ± 9.8	<.001
Female sex (%)	24.6	17.7	46.1	<.001
Race or Ethnic group (%)				
Caucasian	92.1	92.5	88.7	<.001
Black	3.1	2.5	2.9	0.202
Asian/Oriental	3.7	3.9	7.3	<.001
European region (%)	48.4	39.0	42.9	<.001
BMI (mean ± SD)	27.0 ± 5.0	28.5 ± 4.8	28.2 ± 4.9	<.001
Clinical History (%)				
Hypertension	62.8	69.5	74.8	<.001
Hypercholesterolemia	68.5	74.7	67.8	<.001
Heart failure	5.5	6.7	5.8	0.037
Prior MI	34.4	47.3	35.3	<.001
Prior stroke	30.5	24.4	38.8	<.001
Prior TIA	13.2	12.0	17.2	<.001
Diabetes	24.9	31.6	34.3	<.001
Diabetic nephropathy	3.4	4.6	4.6	0.034
PAD	42.3	27.8	12.6	<.001
Prior PCI	20.3	31.1	23.5	<.001
Prior CABG	12.3	26.6	22.2	<.001
Medication (%)				
Aspirin	94.2	96.6	94.4	<.001
Beta blockers	39.6	53.4	49.3	<.001
ARBs	10.6	14.3	16.3	<.001
ACE-inhibitors	53.7	62.8	62.9	<.001
Statins	60.3	70.9	61.5	<.001
Other lipid lowering therapies	6.4	7.4	6.7	0.182
Diabetic medications	21.4	27.7	30.5	<.001
Insulin	7.2	9.4	11.0	<.001
Other oral hypoglycemic agents	16.3	21.6	23.3	<.001

Table 2

Hazard Ratios for death and cardiovascular events according to smoking status

	Unadjusted* hazard ratio (95 percent confidence interval)	Fully adjusted^ hazard ratio (95 percent confidence interval)
All-cause mortality		
Non-smoker	1.00	1.00
Former smoker	1.17 (0.88 – 1.56)	1.25 (0.93 – 1.68)
Current smoker	1.86 (1.36 – 2.56)	2.58 (1.85 – 3.60)
Cardiovascular mortality		
Non-smoker	1.00	1.00
Former smoker	1.16 (0.81 – 1.65)	1.29 (0.90 – 1.84)
Current smoker	1.62 (1.08 – 2.42)	2.26 (1.48 – 3.45)
Cancer mortality		
Non-smoker	1.00	1.00
Former smoker	1.79 (1.07 – 3.00)	2.08 (1.24 – 3.49)
Current smoker	2.26 (1.27 – 4.04)	3.56 (1.96 – 6.46)
Cardiovascular mortality, myocardial infarction or stroke		
Non-smoker	1.00	1.00
Former smoker	0.95 (0.82 – 1.11)	1.00 (0.84 – 1.17)
Current smoker	1.17 (0.97 – 1.41)	1.48 (1.21 – 1.82)
Cardiovascular mortality or myocardial infarction		
Non-smoker	1.00	1.00
Former smoker	1.05 (0.87 – 1.27)	1.00 (0.81 – 1.22)
Current smoker	1.21 (0.96 – 1.52)	1.46 (1.14 – 1.88)
Myocardial infarction		
Non-smoker	1.00	1.00
Former smoker	1.13 (0.87 – 1.48)	0.99 (0.75 – 1.31)
Current smoker	1.19 (0.86 – 1.65)	1.37 (0.96 – 1.95)
Stroke		
Non-smoker	1.00	1.00
Former smoker	0.78 (0.62 – 0.99)	1.09 (0.86 – 1.38)
Current smoker	0.99 (0.74 – 1.31)	1.56 (1.16 – 2.10)
Severe or moderate bleeding		
Non-smoker	1.00	1.00
Former smoker	0.90 (0.71 – 1.14)	1.06 (0.83 – 1.34)
Current smoker	0.97 (0.73 – 1.30)	1.48 (1.09 – 2.00)

* Treatment allocation (clopidogrel versus placebo) was forced into the model. All-cause mortality and cardiovascular mortality were also adjusted for the interaction term between treatment allocation and smoking status.

^ Adjusted for model-selected covariates from the pool of age, sex, ethnicity, geographic region (Europe versus all others), body weight, history of heart failure, hypercholesterolemia, hypertension, diabetes mellitus, diabetic nephropathy, transient ischemic attack, history of myocardial infarction, stroke, peripheral arterial disease, percutaneous coronary intervention, coronary artery bypass graft, and baseline medications (aspirin, beta blocker, ACE-inhibitor, ARB, oral hypoglycemic). Treatment allocation (clopidogrel versus placebo) was forced into the model. All-cause mortality and cardiovascular mortality were also adjusted for the interaction term between treatment allocation and smoking status.